

Cranberry: Health Benefits Supported by Science



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Contributions to Cranberry Health Science for 30 years

- **Discovery and structural ID of unique A-type proanthocyanidins as the active compounds in cranberry that induce bacterial adhesion and contribute to UTI prevention**

Howell et al. 1998. Inhibition of adherence of P-fimbriated *Escherichia coli* to uroepithelial-cell surfaces by proanthocyanidin extracts from cranberries. *The New England Journal of Medicine*

- **Clinical dose-response, analytical methods and comparative testing of dietary supplements**

Howell et al. 2021. Differences in urinary bacterial anti-adhesion activity after intake of cranberry dietary supplements with soluble versus insoluble proanthocyanidins. *Journal of Dietary Supplements*

- **Cranberry's role in prevention of antibiotic resistance**

Howell, A.B, Foxman, B. 2002. Cranberry juice and adhesion of antibiotic-resistant uropathogens. *Journal of the American Medical Association*

- **Other research: Oral cavity health, *H. pylori* suppression, Canine UTI, Esophageal cancer**

Howell, A. 2020. Clinical evidence supporting cranberry as a complementary approach to *Helicobacter pylori* management. *Food Frontiers*

Blueberry and Cranberry Research

RUTGERS

New Jersey
Agricultural Experiment
Station

Philip E. Marucci Center for
Blueberry and Cranberry
Research and Extension

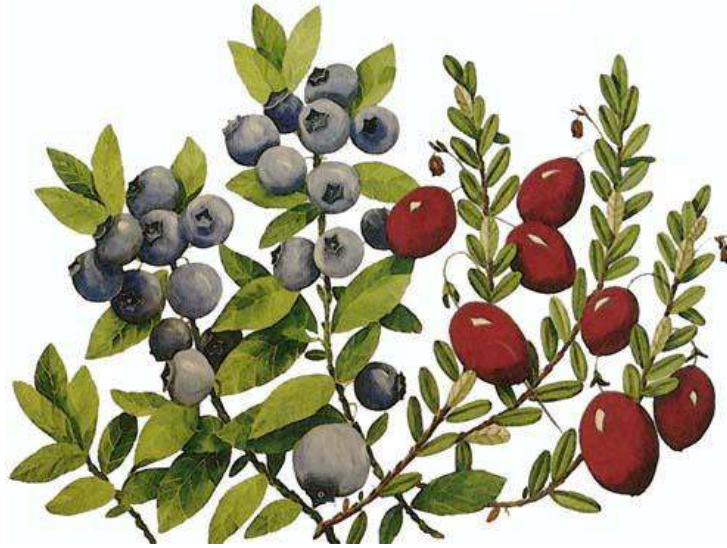
<https://pemaruccicenter.rutgers.edu/>





Blueberries

Cranberries



The genus *Vaccinium*
Grow wild in the NJ Pinelands



American Blueberry
Vaccinium corymbosum



Concord Grape
Vitis labrusca



American Cranberry
Vaccinium macrocarpon

One of only 3 native North American Fruits

Cranberry Production Areas







Research Bog Plots
Marucci Center

Cranberry Products – Processed from “wet harvest” (95% of crop)



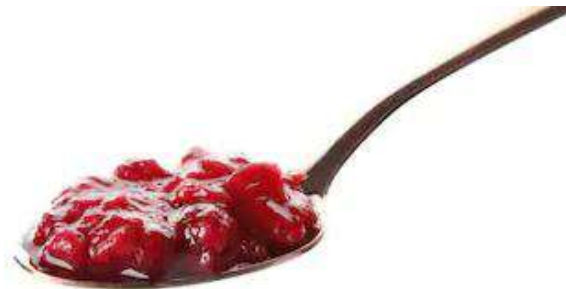
Juice



Dried Fruit



Fruit Powder for
Dietary Supplements



Cooked
Sauce

Cranberry *Considered one of the healthiest fruits*

Urinary tract health

Stomach ulcers

Oral cavity health



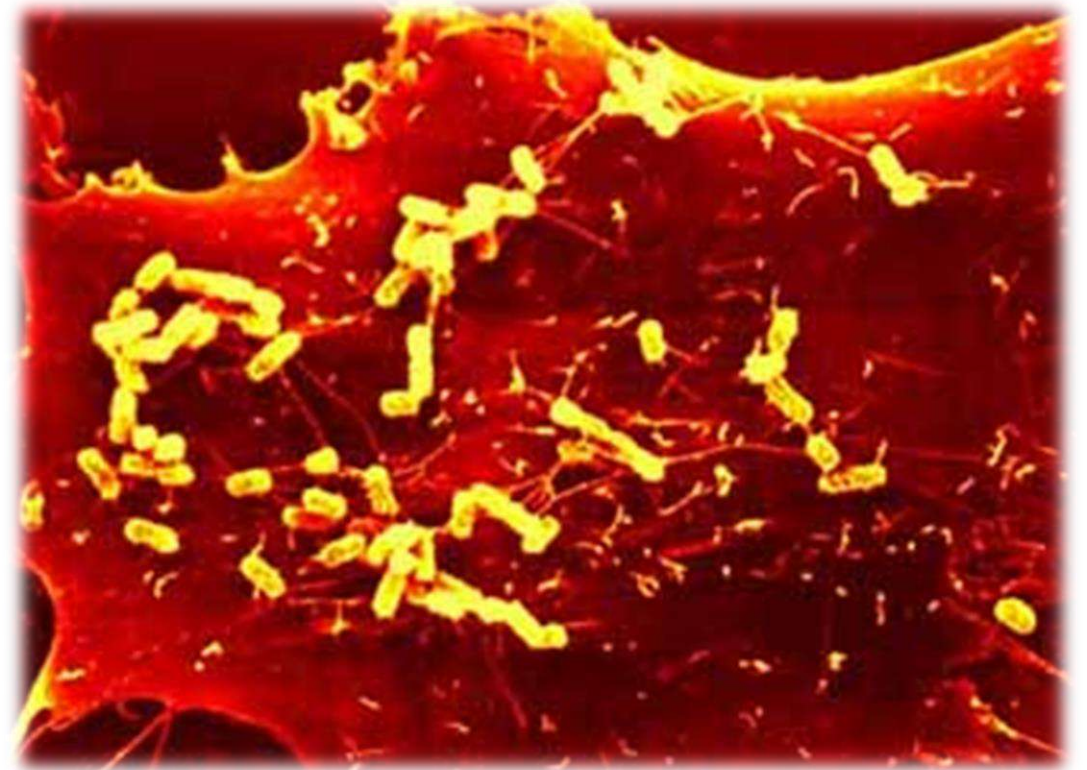
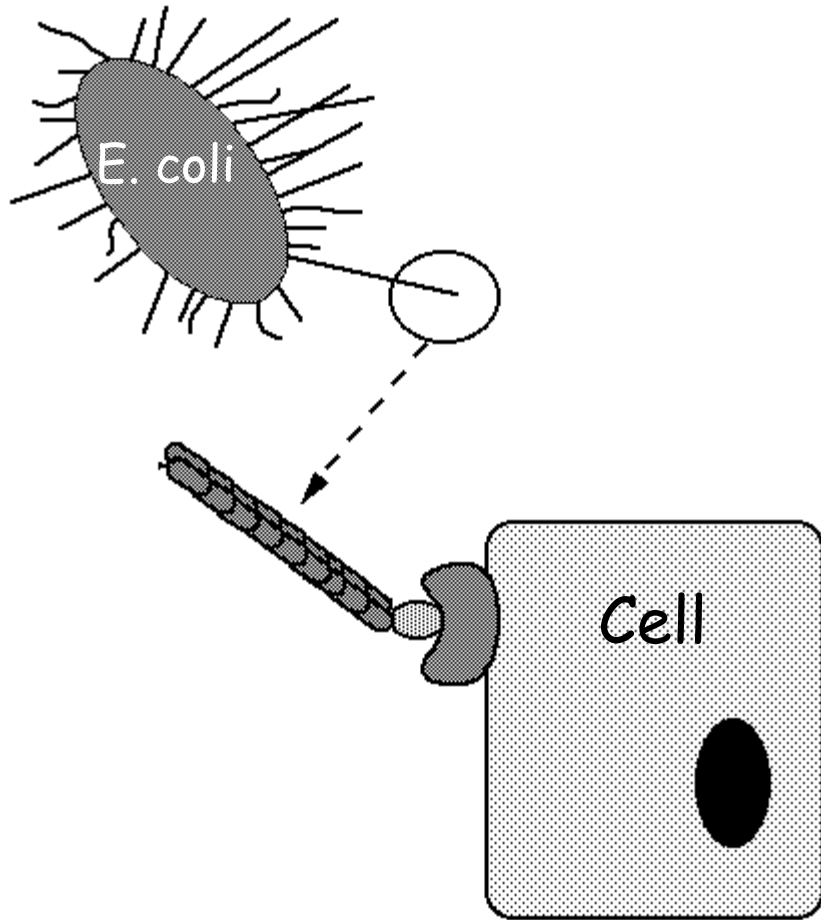
Microbiome/Gut health

**Reduces risk factors
for heart disease**

- Contains over 1000 different active constituents
- Supported by numerous scientific studies and clinical trials

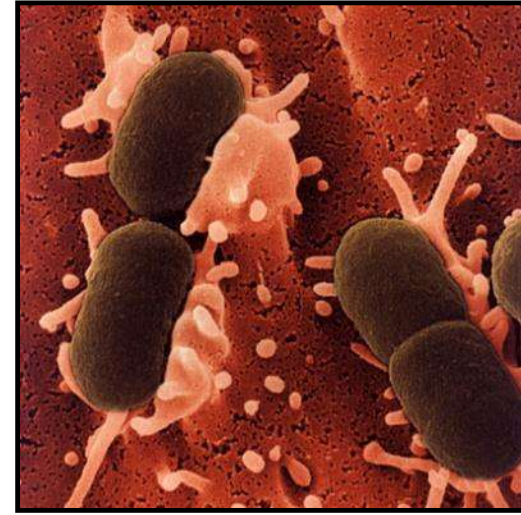
Bacterial Adhesion to Cells

First Step in Bacterial Infection Process



Cranberry prevents bacteria from sticking to cells in the body

It doesn't prevent adhesion of ALL bacteria
Good bacteria from yogurt can keep growing
– That's a good thing!



Bacteria stick to cells \Rightarrow Grow \Rightarrow Infection



Prevents sticking \Rightarrow



Bioactive Compounds in Cranberries

Anthocyanins

- Red fruit pigments
- Protect fruit from UV

Flavonols

- Yellow pigments (flower coloration) attract pollinators
- Pest and insect resistance

Proanthocyanidins

- Condensed tannins
- Astringency
- Plant defense compounds

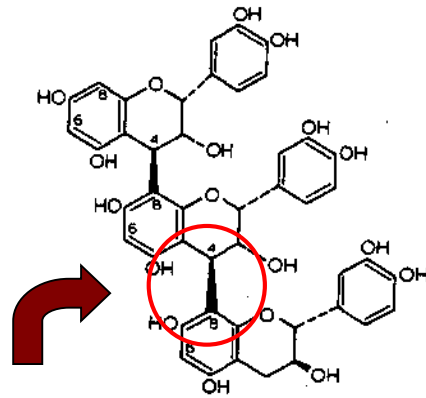
Phenolic Acids

- Odor/flavor characteristics
- Preservatives

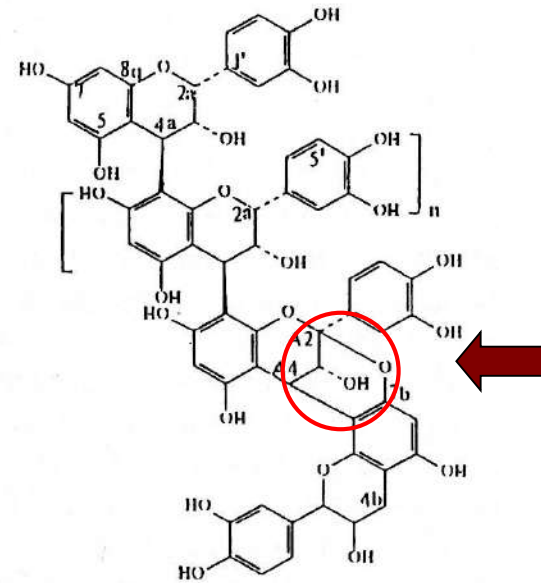


Proanthocyanidins (PACs) found in some other foods

Unusual double A-type bonds in cranberry



B-linked
proanthocyanidin
(grape, chocolate)



A-linked proanthocyanidin
(cranberry)

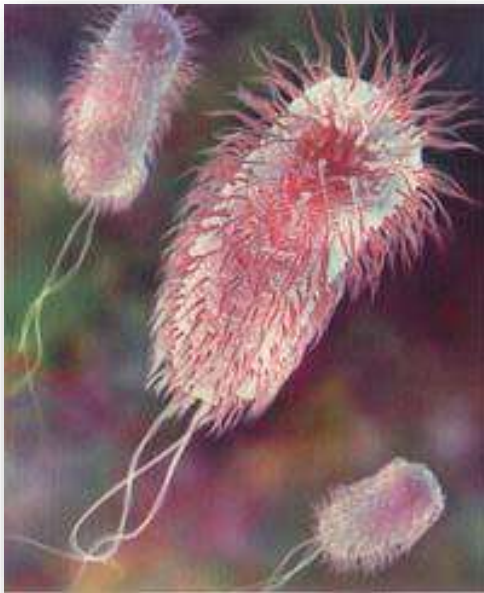


Anti-adhesion activity

Cranberry and Bacterial Infections

Proanthocyanidins (PACs)

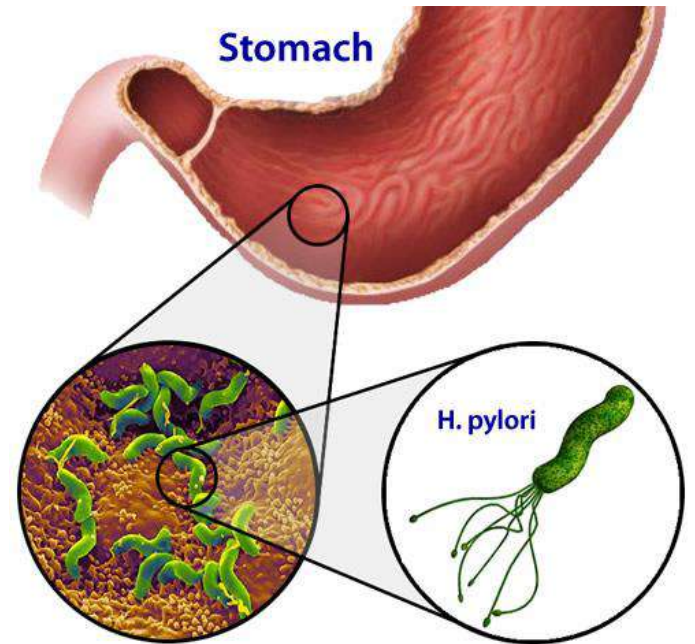
Involved in anti-adhesion at multiple sites



E. coli in Urinary Tract Infection



Bacteria in Periodontal Disease

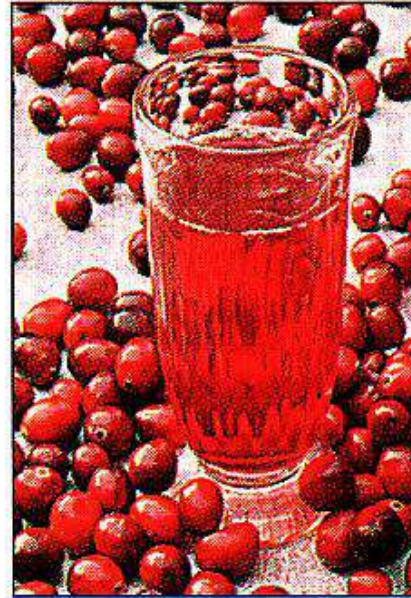


Helicobacter pylori in Stomach Ulcers

A home remedy that works

HEALTH

Doctors have known for years that cranberry juice can be useful in preventing urinary tract infections, which affect 1 in 4 American women. But they didn't know why. A new study has the secret: Cranberries (and blueberries) contain condensed tannins called proanthocyanidins that prevent infection-causing *E. coli* bacteria from attaching to cells in the urinary tract. The findings appeared in last week's *New England Journal of Medicine* and were funded in part by the cranberry juice maker Ocean Spray.



Amy Howell, the study's lead investigator and a research scientist at the Rutgers University Blueberry and Cranberry Research and Extension Center, says the tannins keep infections from developing rather than killing the bacteria, as an antibiotic would.

For women with recurrent urinary tract infections, that means a daily 10-ounce glass of cranberry juice or a fistful of blueberries can provide a safe, preventive approach to avoiding infections. Cranberries with higher concentrations of the tannins are currently being bred.

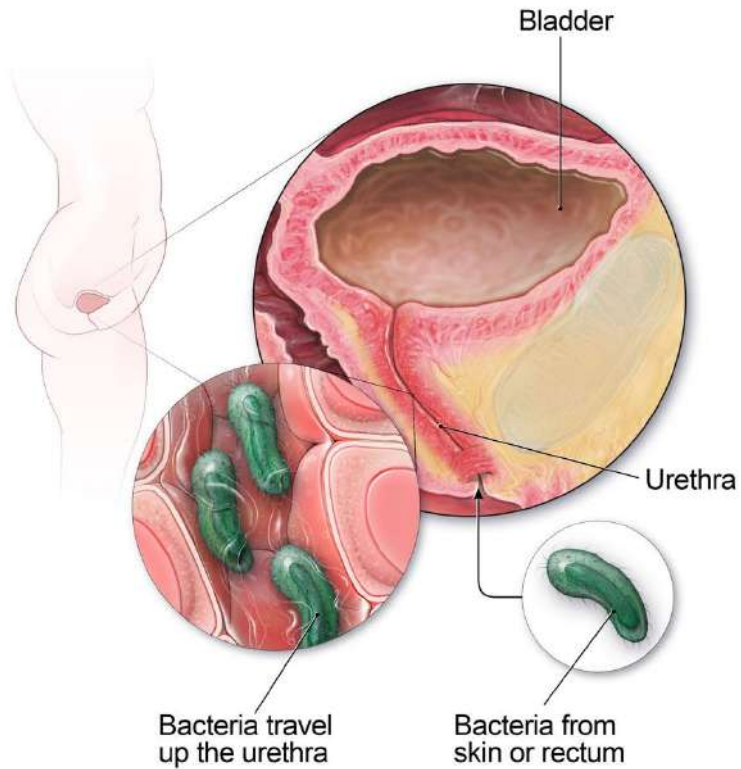
—Stacey Schultz

Howell AB, Vorsa N, Der Marderosian A, Foo LY. Inhibition of the adherence of P-fimbriated *Escherichia coli* to uroepithelial-cell surfaces by proanthocyanidin extracts from cranberries. *N Engl J Med*. 1998 Oct 8;339(15):1085-6

Urinary Tract Infections (UTIs)

Most are caused by *E. coli*
11 million cases/year in U.S.A.

25% recurrence rate



Infected by your own bacteria



Bladder and Kidney UTI

E. coli

Catheter-associated UTI

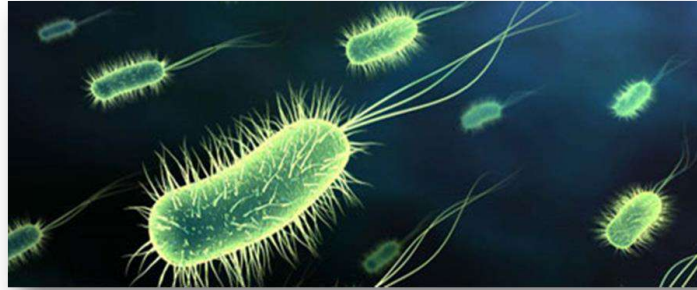
Proteus

Klebsiella

Pseudomonas



Cranberry Consumption and UTI Prevention



- Link to UTI first reported in medical literature in early 1900's

Avorn et al., 1994. *JAMA*. 271(10):751–754.

- Mechanism thought to be due to the acidic pH inducing bacteriostatic effect in urine
- pH theory disproved – bacteriostatic pH rarely achieved in clinical trials with normal serving sizes of cranberry
- Bacteria anti-adhesion is major mechanism of action

Unfortunately, you can't drink wine and eat chocolate to prevent urinary tract infections

They're both rich in PACs



How does cranberry compare?

- 6 healthy volunteers
- Consumed products (3-day wash-out between each)
- Urine collected pre-consumption and every 2 h for 8 h
- Urine tested for bacterial anti-adhesion activity



Single servings of each juice: 240 ml

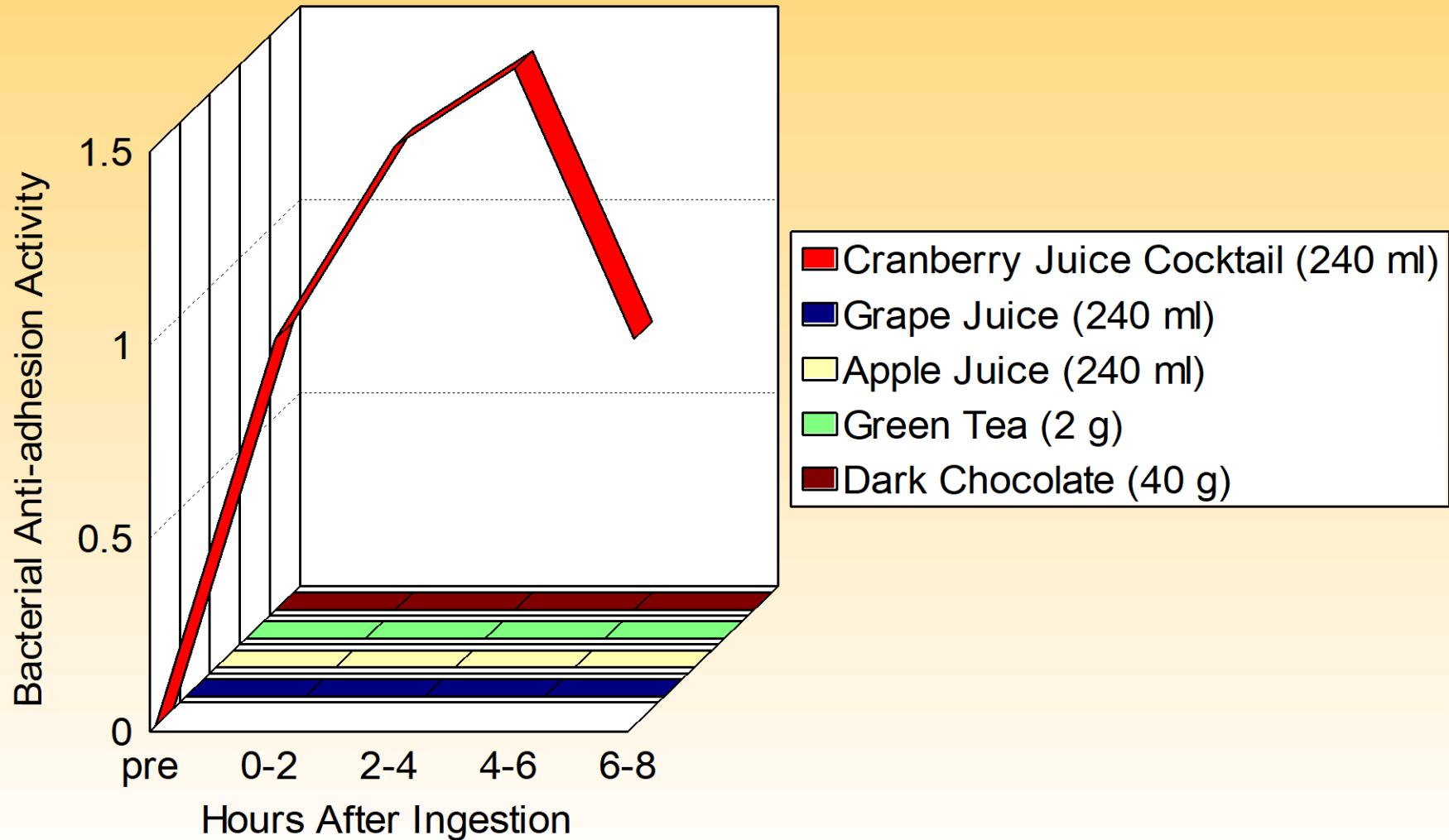


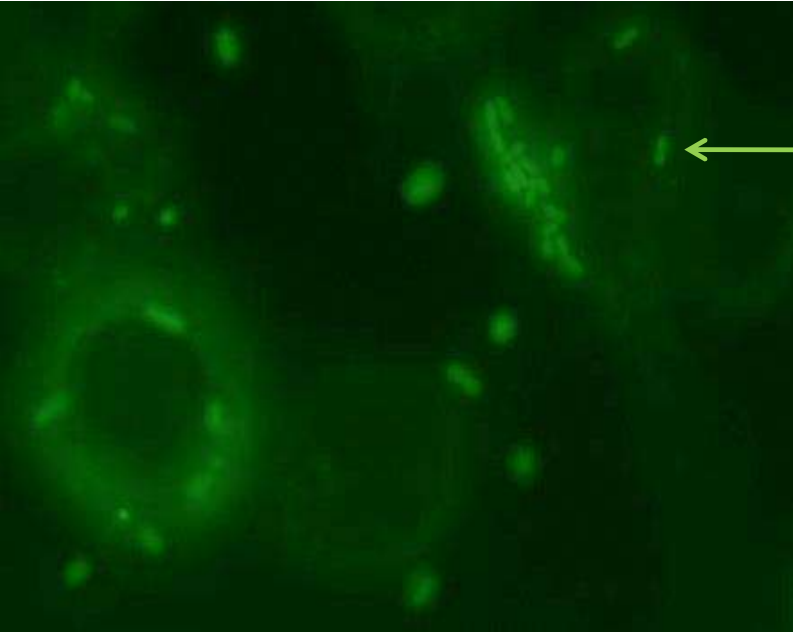
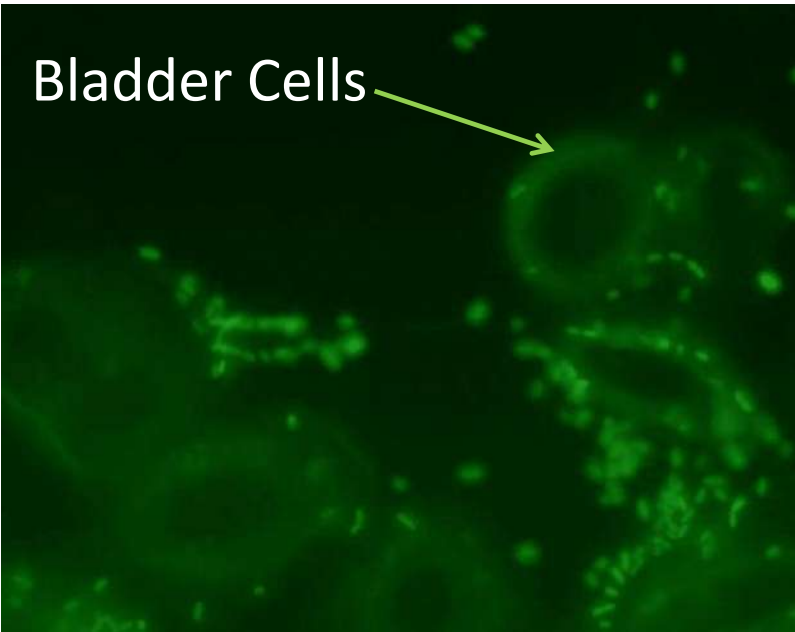
40 g (5 pieces)



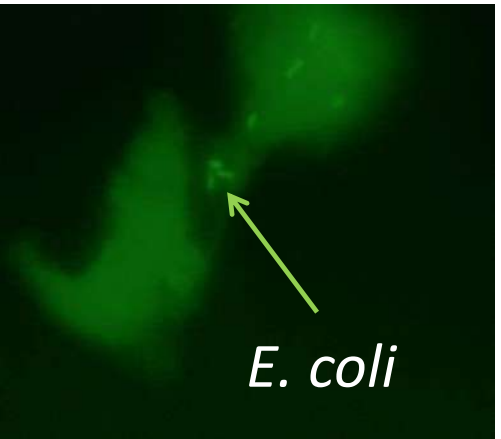
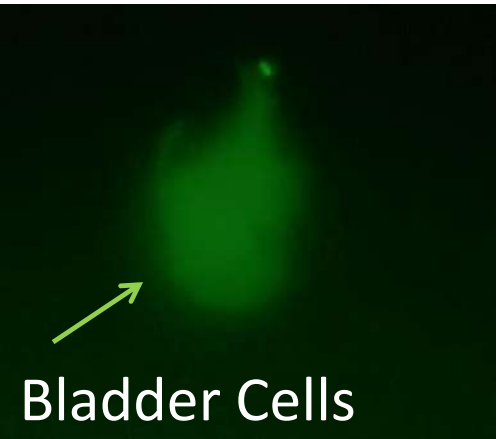
2 g (1 tea bag - brewed)

Anti-adhesion Activity of Human Urine After Cranberry Juice and Other PAC-Products (Single servings)



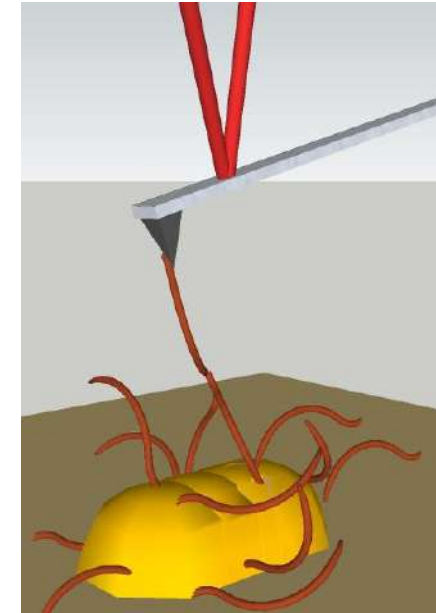
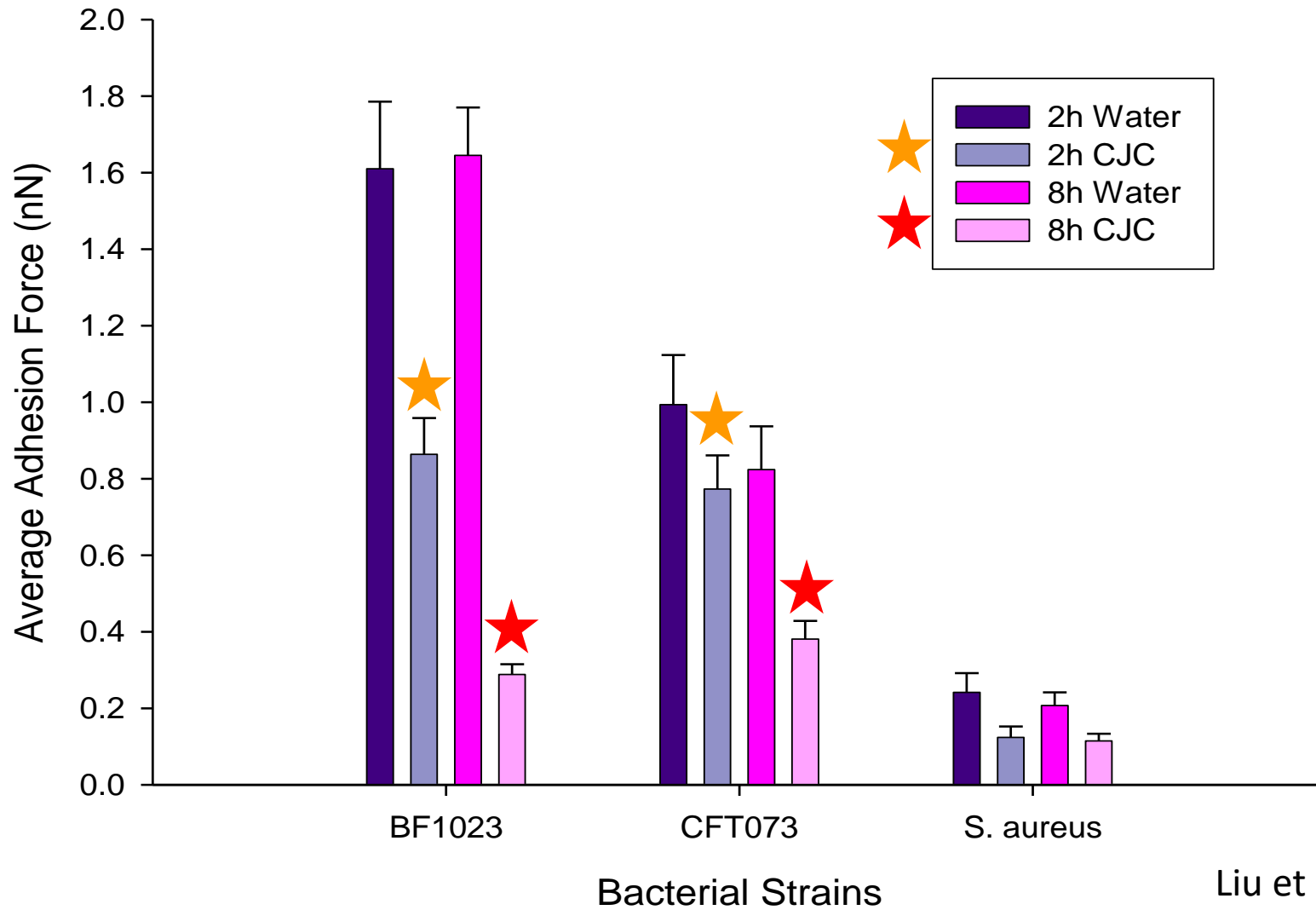


Urine with Bladder Cells and Adhered *E. coli* gfp+



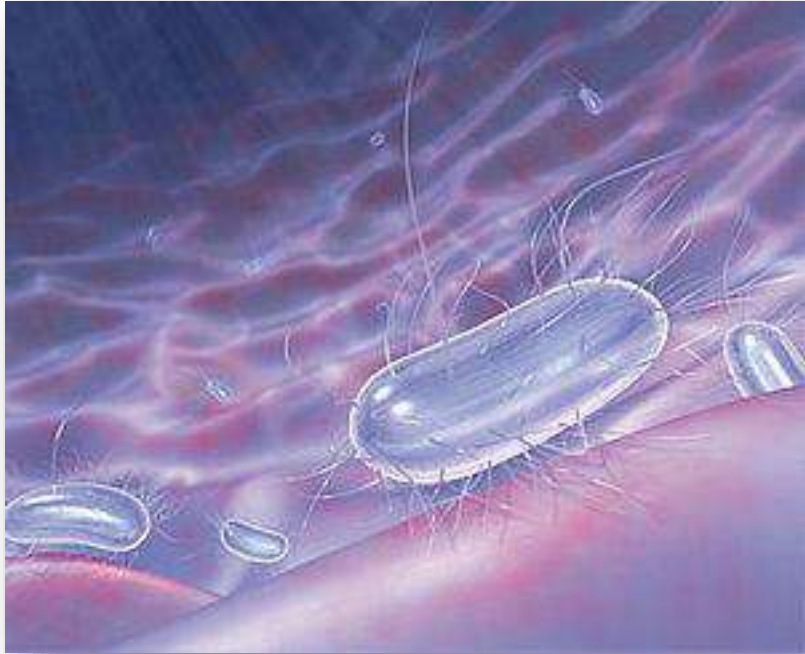
Consuming
cranberry prevents
bacterial adhesion

Adhesion Forces in Urine Reduced After Cranberry Intake

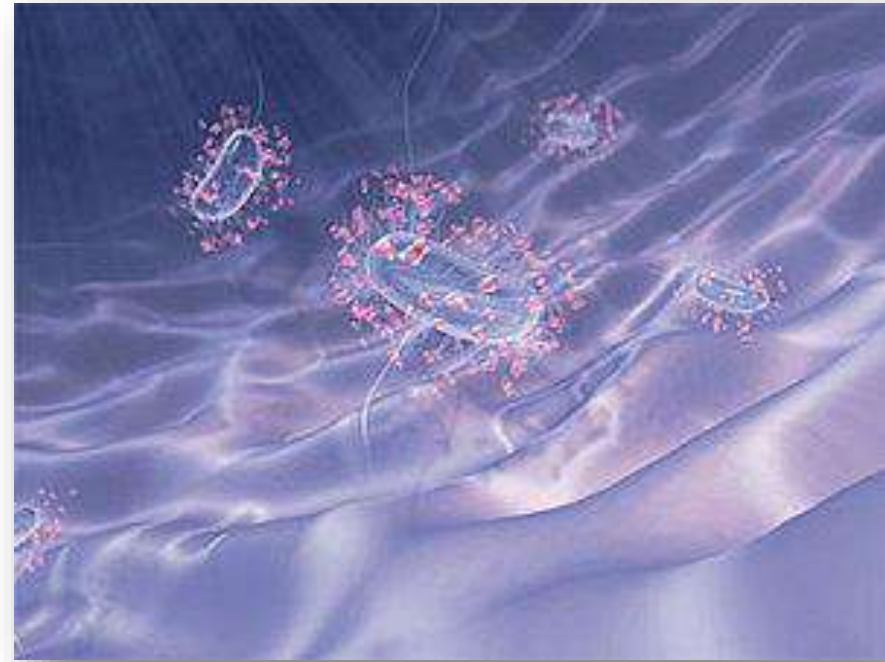


Atomic force microscopy

Unlike antibiotics, bacteria are not killed
but wash out of body in the urine



E. coli bacteria in bladder,
trying to stick to cells



Bacterial hairs blocked by
cranberry compounds

Current Management of UTIs

- Antibiotics used for treatment
- Low-dose antibiotics used for preventing recurrent infections

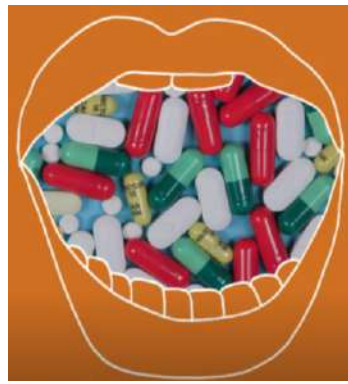


WHO's first global report on antibiotic resistance reveals serious, worldwide threat to public health

New WHO report provides the most comprehensive picture of antibiotic resistance to date, with data from 114 countries



In 1980's,
resistance was
virtually zero



Urinary Tract Infections Affect Millions. The Cures Are Faltering.

As the infections become increasingly resistant to antibiotics, some standard treatments no longer work for an ailment that was once

easily cured

- UTIs are the single biggest risk to healthy people from drug-resistant germs
- A third of all UTIs in Britain are resistant to “key antibiotics”
- UTIs can be food-borne: one crucial path of transfer of germs is **poultry**, which winds up in a person’s gut and can get transferred through fecal residue to the urethra
- In reproductive years, women are 50 X more likely than men to have a UTI. Later in life, the ratio drops to 2 to 1, as men have surgical procedures on their prostate, or catheters, that expose their urinary tracts to infection
- “It can be quite dangerous in this age where there is more and more resistance, and without effective treatment the infection can get into the blood. It can be

E coli from meat behind half a million UTIs in the US every year, study suggests

Fatal bloodstream illnesses driven by urinary tract infections could rise, warn scientists as research shows link to food-borne bacteria



Free-range turkeys are stored inside a refrigerated room at a factory in the UK. Photograph: Bloomberg/Getty Images

Meat bacteria are the likely cause of over half a million urinary tract infections (UTIs) in the US every year, a new study has found, with one of its authors warning that deaths from UTI-driven bloodstream infections could be on the rise.

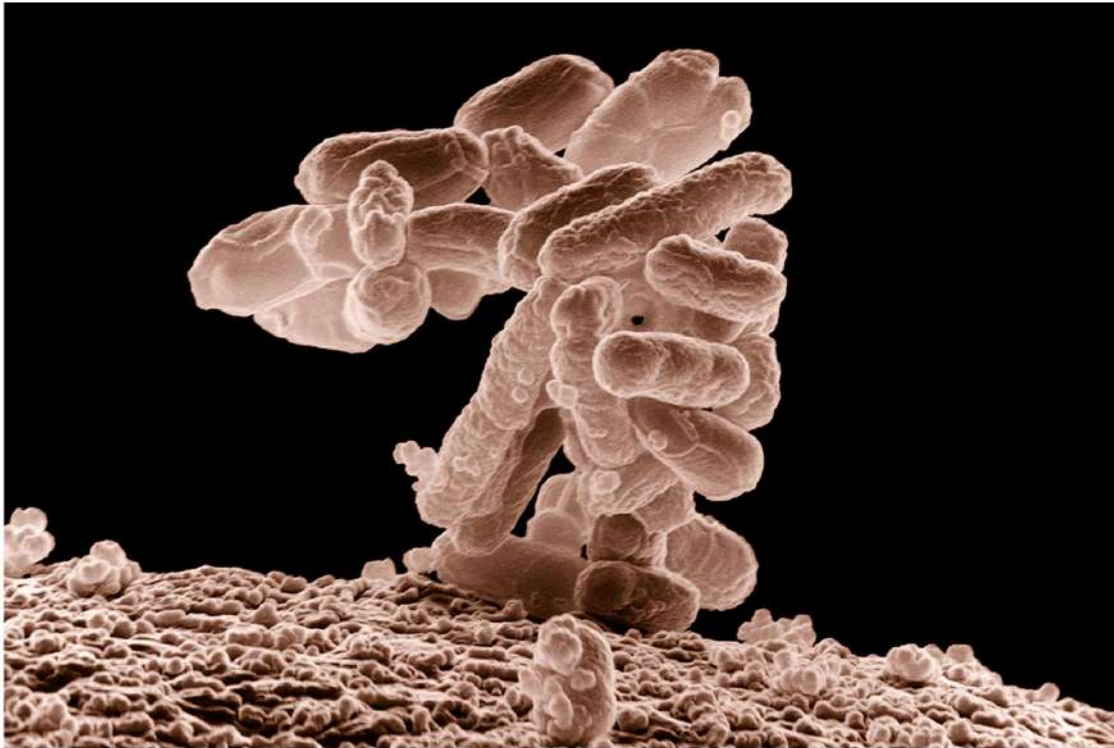
- If left untreated, urinary tract infections caused by *E. coli* can lead to problems like permanent kidney damage, sepsis and a narrowed urethra.
- “Some people think of these as a painful annoyance ... but they can actually be really serious infections because the bladder is actually a gateway to the blood.”

Bloodstream infections are “life-threatening” and those caused by *E. coli* kill 36,000 to 40,000 people a year in the US



SHORT SHARP SCIENCE 27 February 2017

UTIs could soon be life-threatening without new antibiotics



Resistant *E. coli* can make a UTI deadly
Erbe/Pooley/REX/Shutterstock

THE TIMES OF INDIA INDIA

JERSEY SHORE BOAT SALE & EXPO SEPTEMBER 21-23

JERSEY SHORE BOAT SALE & EXPO

Jersey Shore Boat Expo

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UTIs turn fatal with reckless antibiotic use

Durgesh Nandan Jha | Updated: Jun 27, 2017, 05:04 IST



Ad

Jersey Shore Boat Sale & Expo - Sept. 21-23, FirstEnergy Park, Lakewood

This show has something for everyone - hundreds of boats from the state's top dealers.



HIGHLIGHTS

- UTI is one of the most common bacterial infections that affect one or more parts of the urinary system
- It is more common in women than men
- Four to five patients suffer kidney failure due to UTI infection each year

Representative image

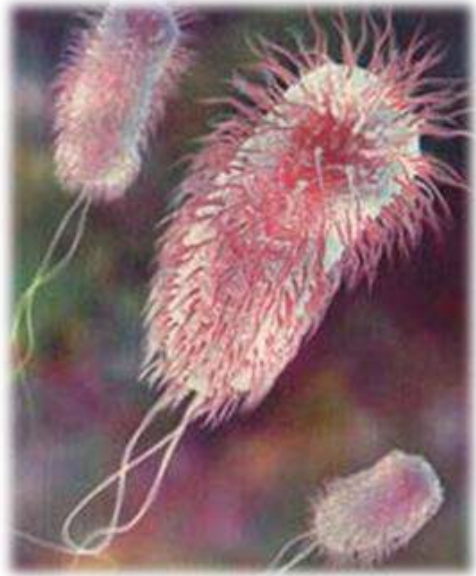
NEW DELHI: Indiscriminate use of antibiotics in India is making common infections like urinary tract infection (UTI) deadly. Urologists say five out of every 10 UTI patients are now requiring injectable drugs and, in some cases, even that fails to help.

"We are forced to use old injectable antibiotics with known toxicity to kidneys, for example Colistin, to save patients with multi-drug resistant UTI," Dr Anup Kumar, professor and head of the urology department at Safdarjung hospital, said.

Antibiotic Resistance Rates Increase with Age

Age Group	N	E. coli Resistance Rate (%)					Trimeth-sulfa	Tetracycline
		Ampicillin	Ciprofloxacin	Nitrofurantoin	Norfloxacin			
< 4	969	60.8	0.9	1.9	1	49.6	33.7	
≥ 4 and < 13	979	57.4	1.5	1	2.1	49.0	32.2	
≥ 13 and < 60	13,675	39.8	7.1	1.6	7.2	29.8	26.6	
≥ 60	7,056	46.1	24.3	5.9	24.4	37.0	37.3	

Anti-adhesion Mechanism Interfering with Initial Step in the Infection Process



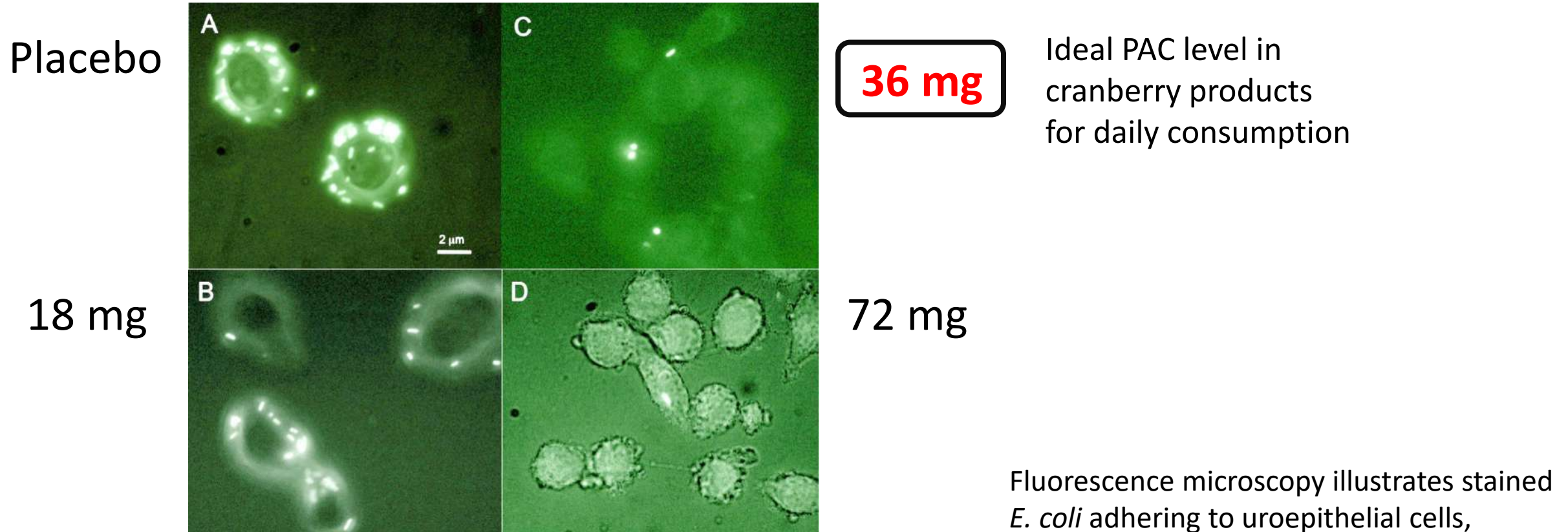
Cranberry intake prevented adhesion of antibiotic resistant *E. coli* in urine by 80%

Greatly reducing selection pressure for proliferation of resistant bacterial strains

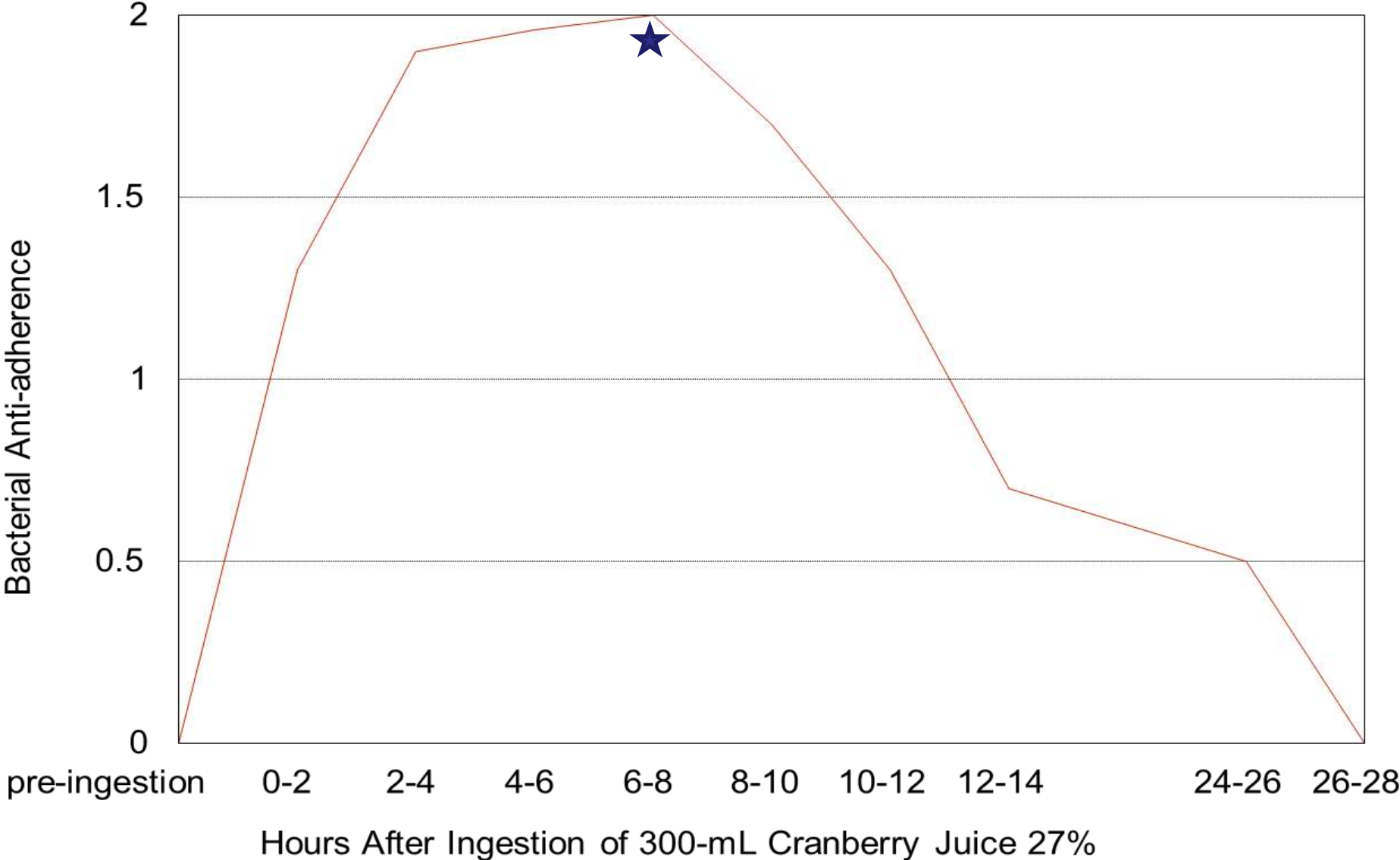
Preventing infections with cranberry could:

- Reduce the subsequent need for antibiotics
- Slow pace of bacterial resistance development to antibiotics

Dose-dependent PACs in Cranberry Achieve Bacterial Anti-adhesion in Urine



Persistence of Urinary Anti-adhesion Activity After Cranberry Intake



Major Clinical Trials – Cranberry and UTI Prevention

Elderly nursing home patients – Cranberry juice (~50% red. bacteriurea) Avorn et al., 1994 *JAMA*

Cranberry powder (significant red. UTI occurrence) Walker et al., 1997 *J. Family Practice*

Cranberry powder (significant red. UTI occurrence) Stothers, 2002 *Can J Urol.*

University women – Cranberry juice (20% red. In UTI risk) Kontiokari et al., 2000 *British Med. J.*

Pregnant women – Cranberry juice (41-57% red. UTI) Wing et al., 2008 *J. Urol.*

Young girls (~50% red. recurrent UTI) Ferrara et al., 2009 *Scand. J. Urol. Nephrol.*

Children (43% red. UTI occurrences) Salo et al., 2011 *Clinical Infectious Diseases*

Women - Cranberry juice (significant red. UTI occurrence) Maki, 2016 *Am J Clin Nutr.*



Three Recent *Positive* Meta-analyses for Cranberry in Reducing UTI Incidence

Cranberry Reduces the Risk of Urinary Tract Infection Recurrence in Otherwise Healthy Women: A Systematic Review and Meta-Analysis.

Fu et al., *Journal of Nutrition*, 2017

Can Cranberries Contribute to Reduce the Incidence of Urinary Tract Infections? A Systematic Review with Meta-Analysis and Trial Sequential Analysis of Clinical Trials.

Luis et al., *Journal of Urology*, 2017

Effectiveness of Cranberry Ingesting for Prevention of Urinary Tract Infection: A Systematic Review and Meta-analysis of Randomized Controlled Trials.

Huang et al., *Journal of Medicine and Pharmaceutical Sciences*, 2017

Cranberries vs Antibiotics to Prevent UTIs

Prevention of UTI for 12 months with low-dose antibiotic or cranberry

- High resistance rates after just 1 month of antibiotic use

Resistance to TMP/SMX, trimethoprim and amoxicillin increased from 21-28% to 73-91% in both feces and urine

Resistance in urinary *E. coli* isolates increased from 8% at baseline to 23% after 12 months of TMP/SMX

- Cranberry almost as effective as low-dose antibiotics, but preferred due to absence of substantial antibiotic resistance issues

Pediatric Trials with Cranberry: Reduced UTI Incidence and Less Antibiotic Use



40 children, cranberry juice vs placebo: 65% reduction in UTI incidence

Afshar et al., *J Urol*. 2012 188(4 Suppl):1584-7

84 girls, 50 ml cranberry juice or controls for 6 mo: lower UTI incidence (18.5%) compared to placebo (48.1%)

Ferrara et al., *Scandinavian J Urol Nephrol*, 2009. 43(5): 369-372

263 children, cranberry juice or placebo for 6 mo: Lower incidence density (27 vs 47), decreased number of days on antibiotics (12 vs 18)

Salo, *Clin Infect Dis*, 2012. 54(3): 340-346

How much cranberry each day for UTI prevention benefits?

- Cranberry juice cocktail 8-10 ounces
(Regular or “Light”)
- Dried cranberries ½ cup
- Cranberry sauces ¼ cup
- Cranberry powders (capsules) 240–2000 mg



FDA Qualified Health Claim for Cranberry and UTI Prevention

Buyer Beware – Shop Smart!

To the bladder
and beyond!

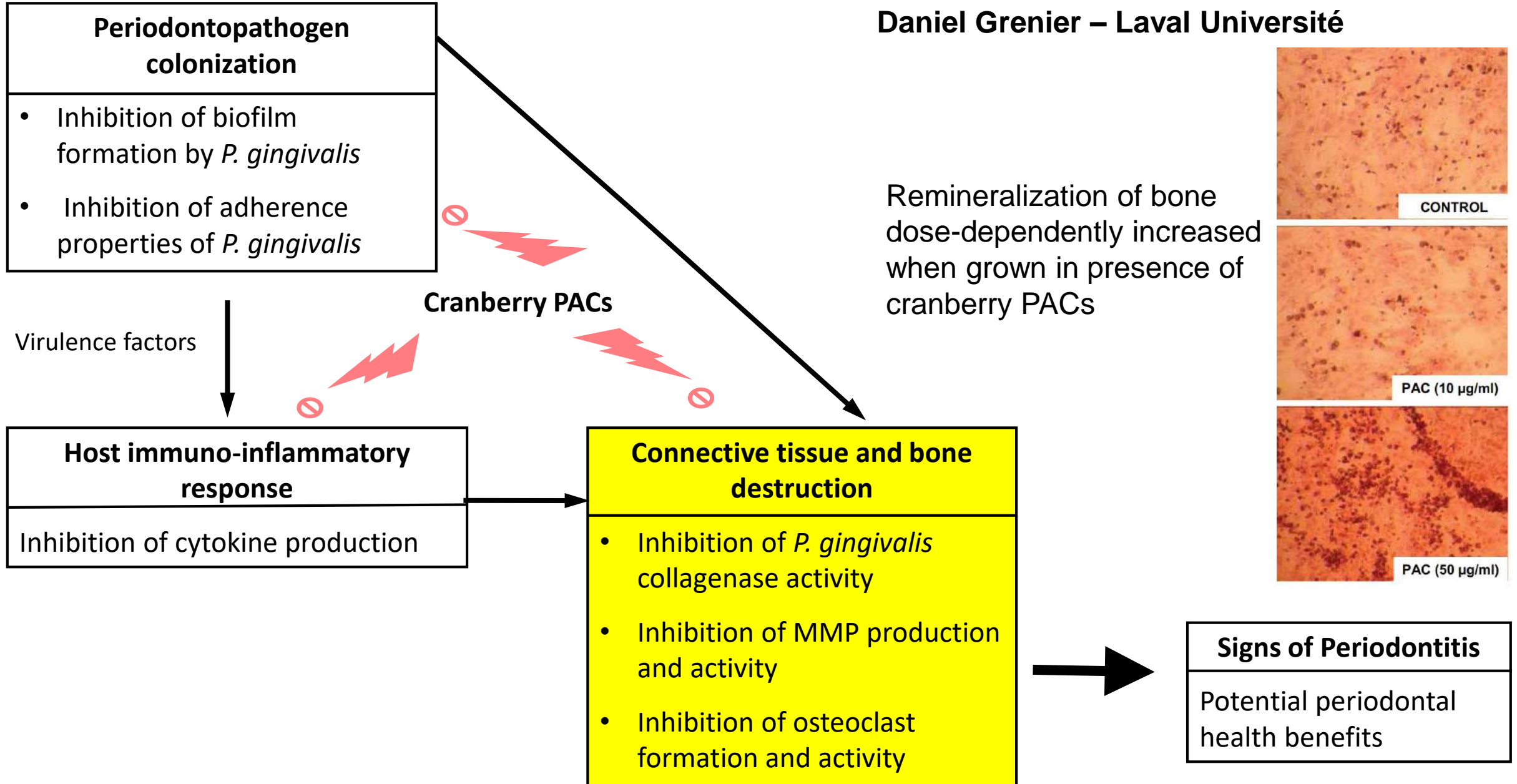




- Cranberry PACs significantly reduced incidence and severity of cavities, may have value as a supplement to fluoride for dental caries prevention
- Cranberry PAC-based mouthwash significantly reduced salivary bacterial counts after 6 weeks of use, inhibiting adhesion of *Streptococcus mutans* and *S. sobrinus* and promoting desorption of bacteria from biofilms, reducing plaque
- Inhibited *S. mutans* enzyme activity and bacterial acid production – mechanism related to PAC A-type linkage rigidity
- Cranberry PACs disrupt these cariogenic virulence properties without being bactericidal, retaining benefits of symbiotic resident oral microbiome and preventing emergence of resistant microbes

Cranberry PACs and Periodontal Disease

Daniel Grenier – Laval Université



Developing Cranberry PAC Oral Health Products

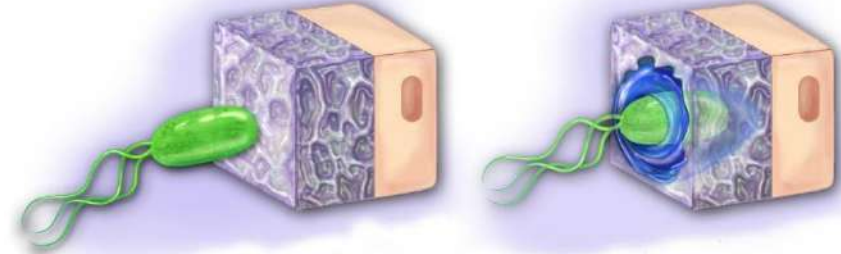
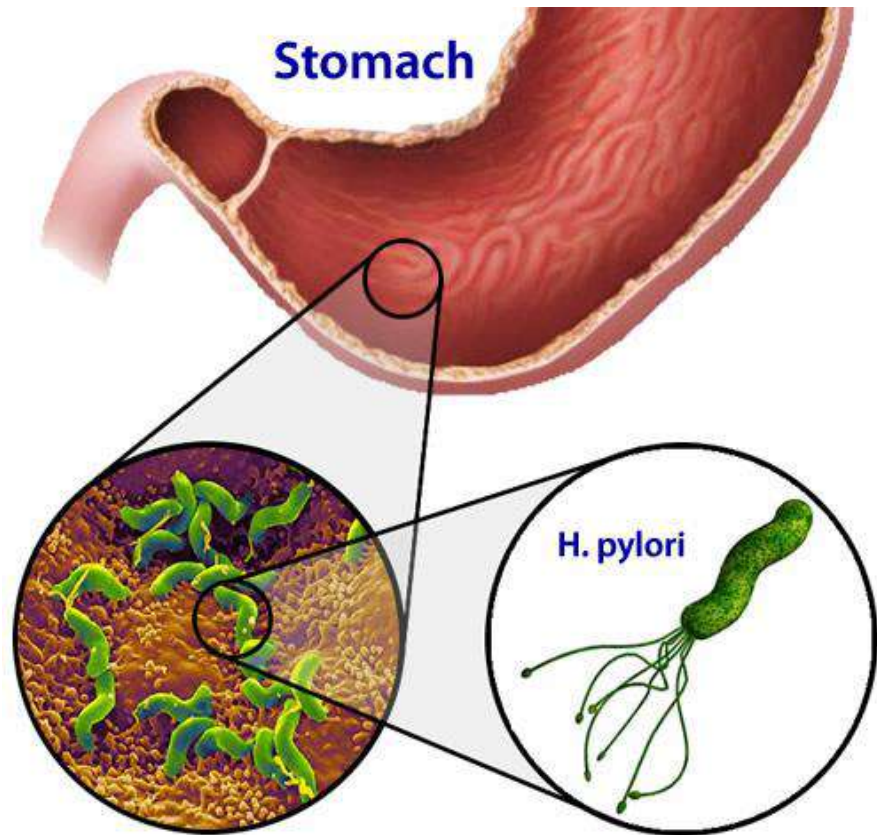
Product development with cranberry PAC
Not whole cranberry
(acid not good for teeth)



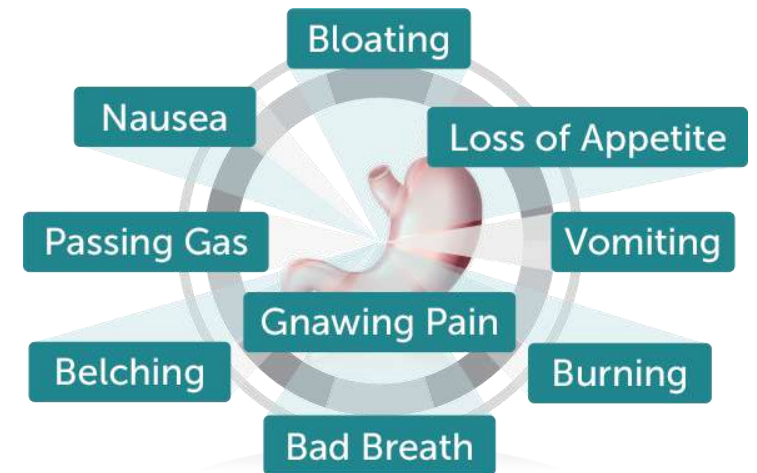
Need adequate “contact time” on teeth and gums

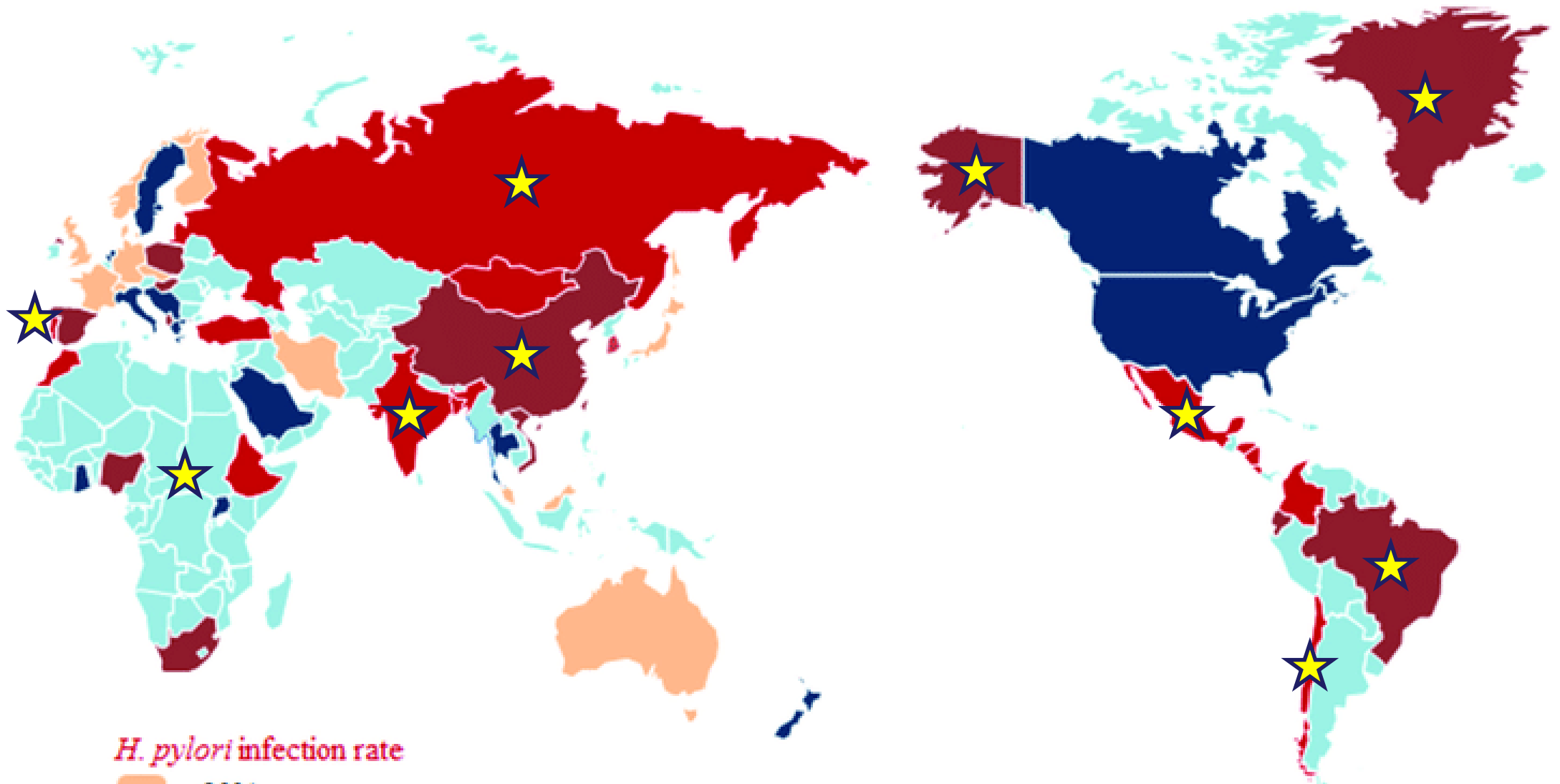


Stomach Ulcers Caused by Bacteria (*H. pylori*)



- Bacteria dissolve stomach lining and attach to stomach cells
- Stomach cells exposed directly to stomach acids
- Results in an ulcer





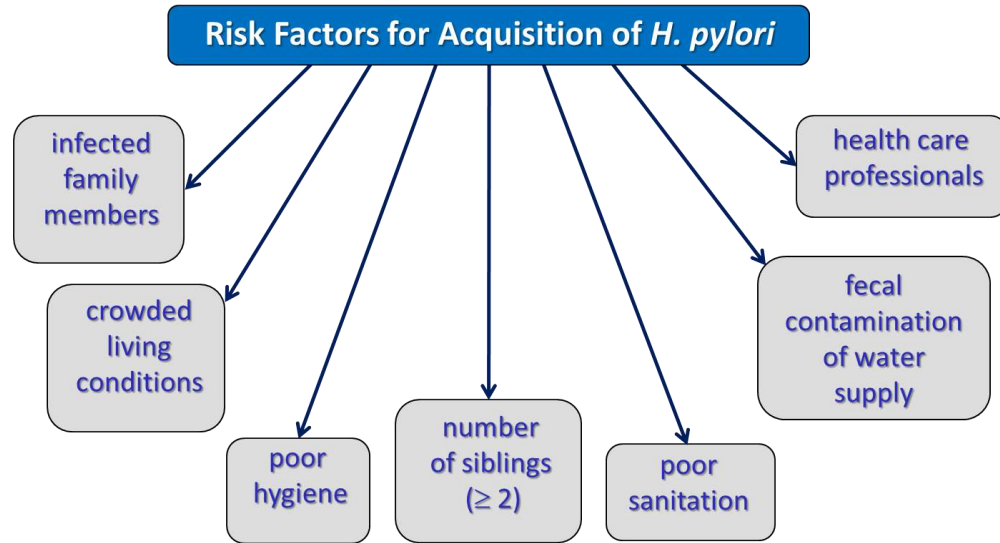
H. pylori infection rate

- <30%
- 30-50%
- 50-70%
- >70%
- Unclear

2/3 of the World is infected with *H. pylori*

Very Difficult to Treat and Eliminate *H. pylori* Bacteria

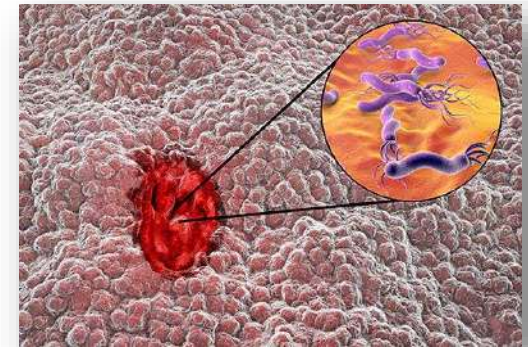
Highly Contagious



- Antibiotic treatments (2 or 3)
- Don't always work
- Antibiotic resistance high
- Bad side effects
- Destroy good gut bacteria

Dangerous Bacteria:

If infections are not treated, risk of developing lower stomach cancer increases (3- to 6-fold)



“Diet-based treatment could reduce levels of colonization and reduce gastritis and cancer risk-factors without completely eliminating the bacteria” (Fahey et al., 2015, Nutrition Res.)

Cranberry Juice Suppresses *H. pylori* Infections (Recent clinical trial study with over 500 people)

Cranberry compounds prevent
H. pylori bacteria from attaching
to stomach lining



100% Pure Cranberry Juice: ½ cup taken twice daily for at least 8 weeks

- Can dilute in other juices or carbonated water to improve palatability
- No side effects or health risks

Not a substitute for antibiotics, but a complementary approach to managing infections and retaining good gut bacteria

GASTROENTEROLOGY

Suppression of *Helicobacter pylori* infection by daily cranberry intake: A double-blind, randomized, placebo-controlled trial

Zhe-Xuan Li,* Jun-Ling Ma,* Yang Guo,* Wei-Dong Liu,† Ming Li,† Lan-Fu Zhang,† Yang Zhang,* Tong Zhou,* Jing-Ying Zhang,* Ha-Er Gao,* Xiao-Ying Guo,* Dong-Man Ye,‡ Wen-Qing Li,* Wei-Cheng You* and Kai-Feng Pan*

*Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Cancer Epidemiology, Peking University Cancer Hospital & Institute, Beijing†Department of Medical Imaging, Liaoning Cancer Hospital & Institute, Cancer Hospital of China Medical University, Shenyang, and ‡Office for Gastric Cancer Prevention, Linqu County Public Health Bureau, Shandong, China

Key words

Cranberry, *Helicobacter pylori*, Randomized clinical trial, Suppression.

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Declaration of conflict of interest: None.

Author contribution: Z-X. L. and K-F. P. made the study design. Z-X. L. and K-F. P. drafted the manuscript. Z-X. L., Y. G., and K-F. P. performed the statistical analyses and interpretation. Y. G. carried out the randomization. All the rest of the authors have contributed to data acquisition and critical review of the manuscript. All authors approved the final version of the article, including the authorship list.

Financial support: This study was supported by a grant from the Cranberry Marketing Committee (CMC) sanctioned by the USDA-AMS.

Guarantor of the article: Zhe-Xuan Li and Kai-Feng Pan.

Abstract

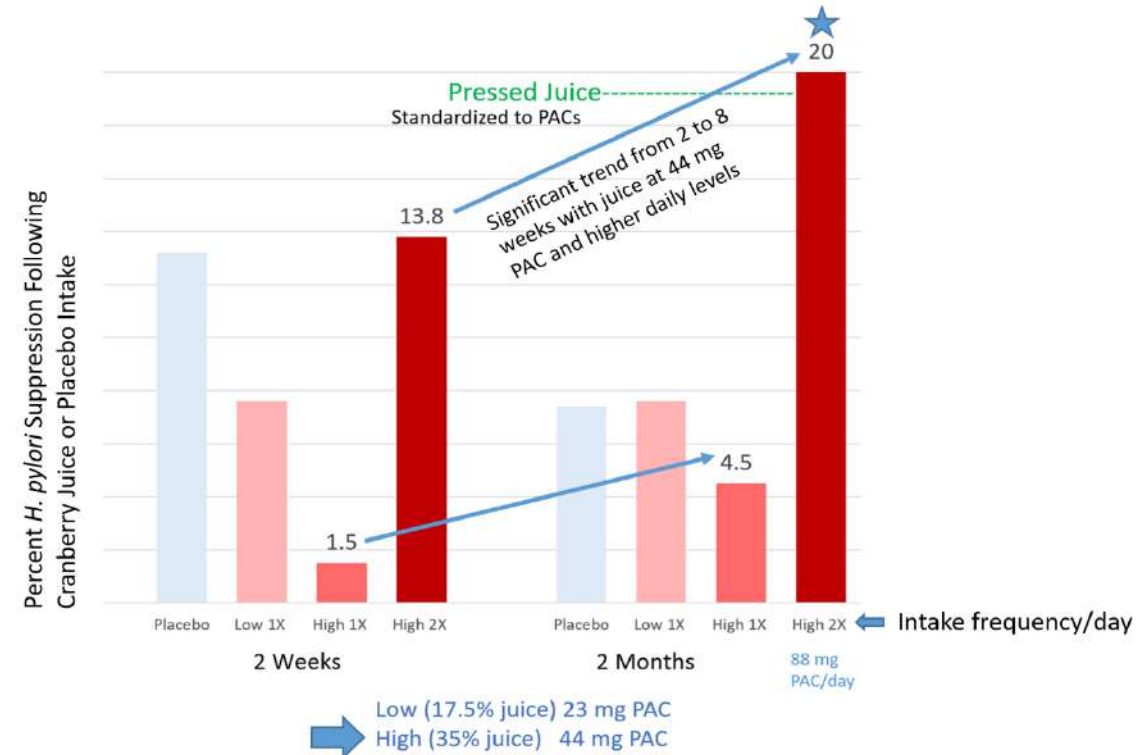
Background and aim: Dietary strategies that contribute to reducing incidence of *Helicobacter pylori* infection without negative side effects are highly desirable owing to worldwide bacterial prevalence and carcinogenesis potential. The aim of this study was to determine dosage effect of daily cranberry consumption on *H. pylori* suppression over time in infected adults to assess the potential of this complementary management strategy in a region with high gastric cancer risk and high prevalence of *H. pylori* infection.

Methods: This double-blind, randomized, placebo-controlled trial on 522 *H. pylori*-positive adults evaluated dose–response effects of proanthocyanidin-standardized cranberry juice, cranberry powder, or their placebos on suppression of *H. pylori* at 2 and 8 weeks by ¹³C-urea breath testing and eradication at 45 days post-intervention.

Results: *H. pylori*-negative rates in placebo, low-proanthocyanidin, medium-proanthocyanidin, and high-proanthocyanidin cranberry juice groups at week 2 were 13.24%, 7.58%, 1.49%, and 13.85% and at week 8 were 7.35%, 7.58%, 4.48%, and 20.00%, respectively. Consumption of high-proanthocyanidin juice twice daily (44 mg proanthocyanidin/240-mL serving) for 8 weeks resulted in decreased *H. pylori* infection rate by 20% as compared with other dosages and placebo ($P < 0.05$). Percentage of *H. pylori*-negative participants increased from 2 to 8 weeks in subjects who consumed 44 mg proanthocyanidin/day juice once or twice daily, showing a statistically significant positive trend over time. Encapsulated cranberry powder doses were not significantly effective at either time point. Overall trial compliance was 94.25%. Cranberry juice and powder were well-tolerated.

Conclusions: Twice-daily consumption of proanthocyanidin-standardized cranberry juice may help potentiate suppression of *H. pylori* infection. Trial registration: ChiCTR1800017522, per WHO ICTRP.

Statistically significant 20% suppression of *Hp* with cranberry juice containing 44 mg PAC taken morning and evening



Dose-response using different cranberry product forms containing increasing PAC levels given either once or twice daily

More definitive than previous clinical results that used single servings of non-standardized cranberry juices given once daily

Cranberry powder not effective – dissolution issues?

China's population: 1.4 billion

70% *Hp* infection rate: 980 million

20% develop stomach cancer: 196 million



Stomach cancer: 3rd leading cause of cancer deaths in China

Accounts for >40% of all new gastric cancer cases worldwide



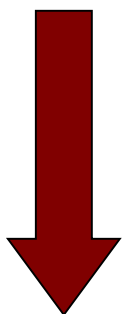
Cardiovascular Benefits

Heart Disease...

It's all about

Improving Blood Flow

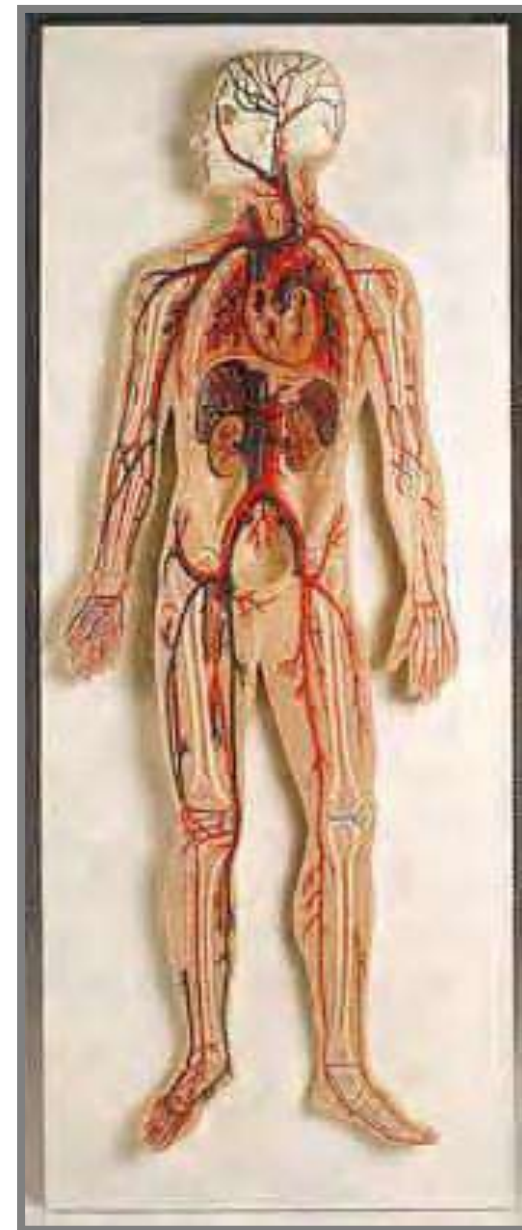
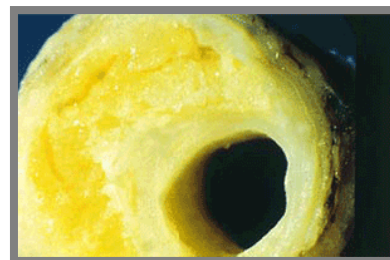
Cranberries



Inflexibility of arteries

LDL cholesterol oxidation

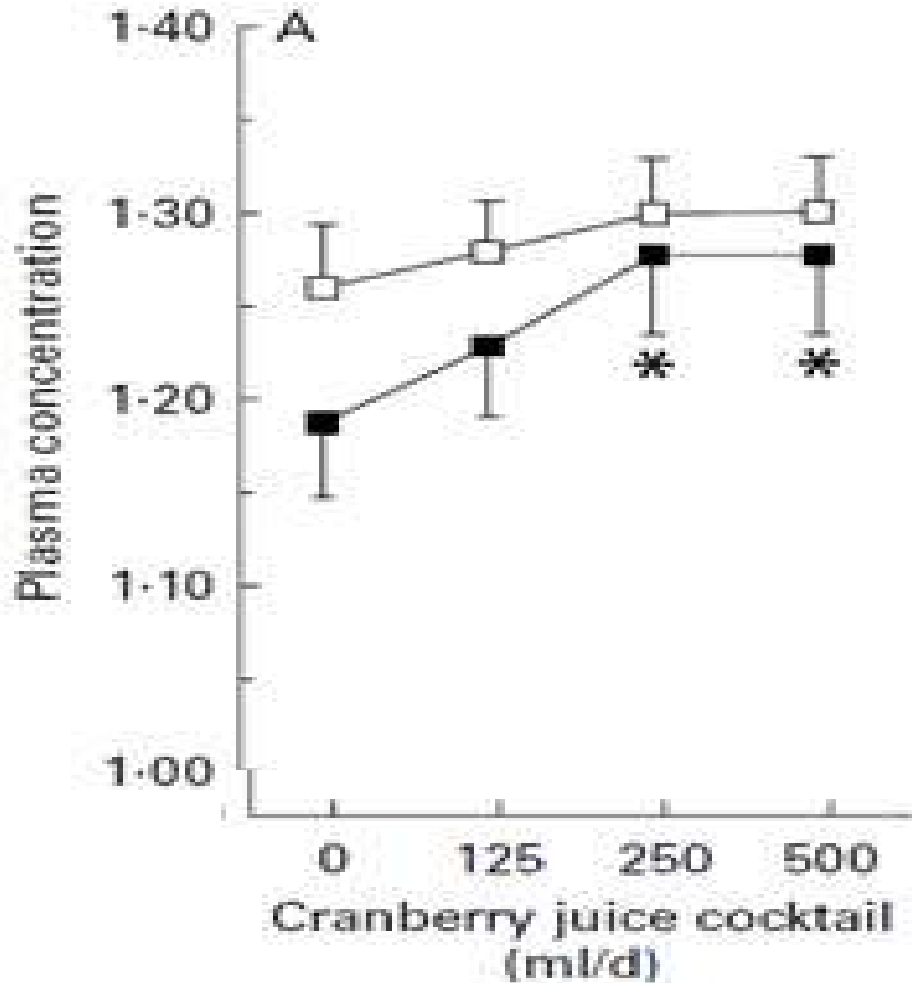
Inflammation (similar to aspirin – inhibit COX-2 expression, decreases proinflammatory prostaglandin synthesis)



Cranberry increases plasma HDL-cholesterol concentrations in men

Couillard - Laval University

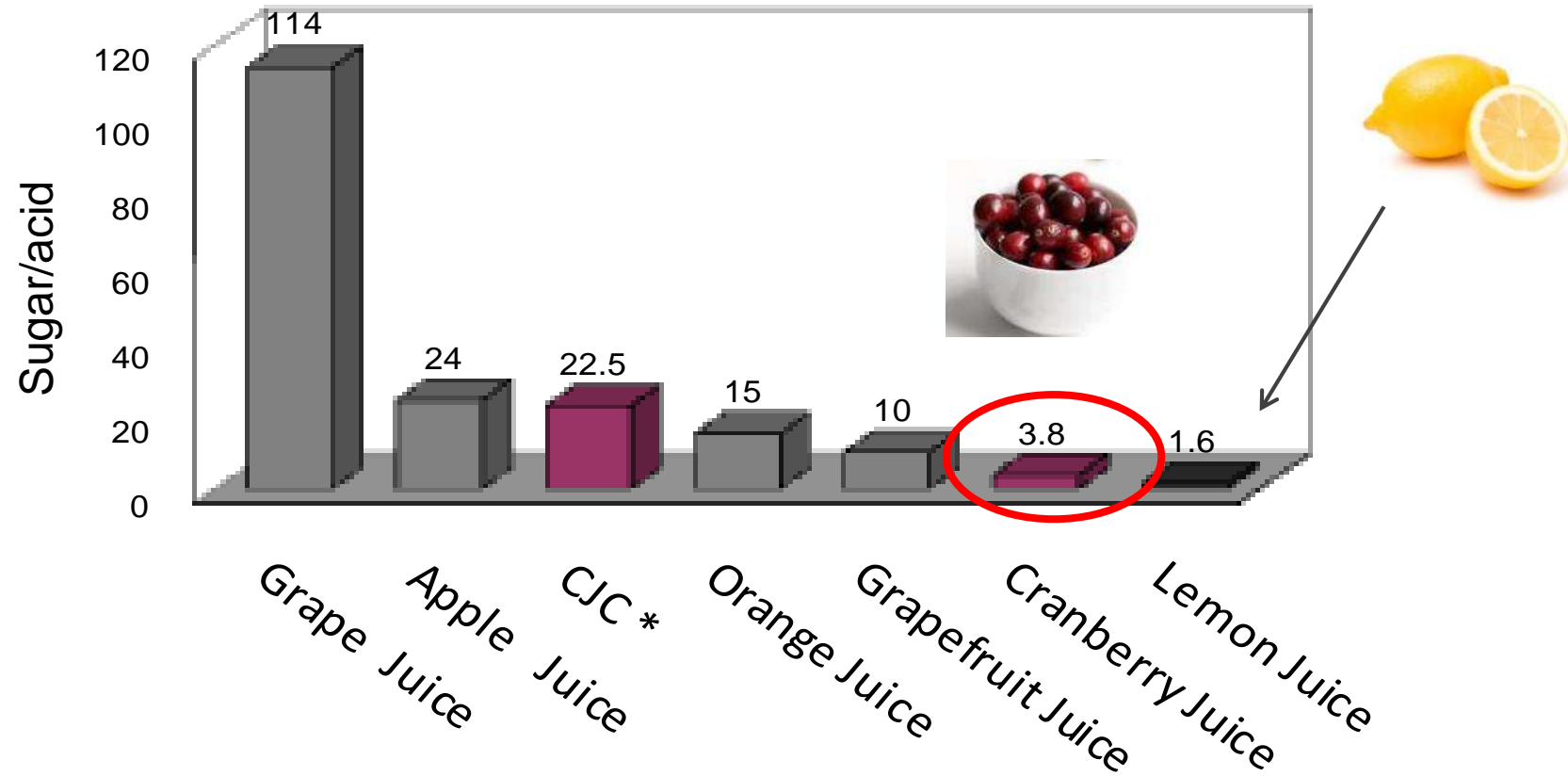
Changes in plasma HDL-cholesterol (mmol/l)



- Abdominally obese men
- Increasing doses, 4 wks each
- 250mL Light CJC/day
- 8.6% increase in HDL
- Drugs ~ 10% increase

Cranberry Dilemma:

Powerful and Unique Health Benefits...
But with Low, Naturally Occurring Sugar



* CJC cranberry juice cocktail (27% cranberry)

The amount of sugar in dried cranberries is equal to that of other dried fruits, like raisins and dried cherries

Dried cranberries are a good source of fiber

– 10% of the Daily Value – with 2.3 grams per serving (40 grams)



Product Diversity

Cranberry as an ingredient



Incentives to Utilize Cranberry for Health Promotion



- Reduced antibiotic resistance issues
- Inexpensive, convenient functional food
- Effective at reasonable serving sizes
- Additional health benefits possible
 - Anti-adhesion in other sites in the body
 - Antioxidant/anti-inflammatory/heart health

Review Article on Cranberry Health Benefits

Cranberries and Their Bioactive Constituents in Human Health

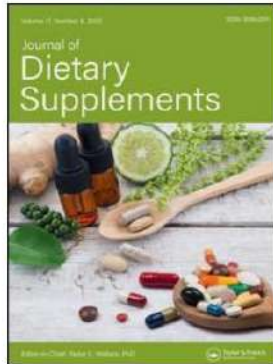
Information about the bioactive compounds in cranberry and how they may protect against UTIs, cardiovascular health, etc.

Blumberg et al. 2013. Cranberries and their bioactive constituents in human health. *Advances in Nutrition* 4(6):618-32

<http://advances.nutrition.org/content/4/6/618.full>

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Selecting an Effective Cranberry Supplement



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Differences in Urinary Bacterial Anti-Adhesion Activity after Intake of Cranberry Dietary Supplements with Soluble versus Insoluble Proanthocyanidins

Amy B. Howell, Jean-François Dreyfus & Bilal Chughtai

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Any Questions?

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